REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. Status Of Claims And Formal Matters

Claims 1-20 are under consideration in this application. Claim 1 was amended and claims 2 and 6 were cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Applicants reserve the right to pursue the subject matter of cancelled claims in continuing application.

Support for the recitation of a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus A is found throughout the specification, for example on page 16, lines 1-3 and in Example 2. Support for a gene encoding a fusion protein comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody is found throughout the specification, for example on page 27, lines 2-8 and in Example 6.

No new matter has been added.

It is submitted that the claims herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§101, 102, 103 or 112. Rather, these additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action rejects claims 1-3, 5-10, and 12-18 for allegedly lacking enablement on the basis that the specification fails to provide sufficient guidance teaching how to make or use any adenovirus with (i) a gene encoding a heterologous protein, (ii) a modified fiber protein comprising an immunoglobulin-binding domain, and (iii) a gene encoding a fusion protein comprising a targeting ligand and an immunoglobulin Fc domain. Furthermore, the Office Action alleges that the claims are very broad in that they encompass any recombinant adenovirus

with (i) any gene encoding a heterologous protein, any modified fiber protein comprising any immunoglobulin-binding domain, and/or (iii) any fusion protein comprising a targeting ligand for any cell surface molecule. In addition, the Office Action states that an analysis of the prior art as of the effective filing date of the instant application shows the complete lack of documented success for in vivo adenovirus targeting; that the specification fails to teach whether proper virion assembly would occur; it does not indicate whether correct protein folding would result; and that there is no art of record for the successful genetic re-targeting of an Ad vector comprising a genetically modified fiber protein used in conjunction with an adapter molecule produced by the same Ad vector, either in vivo or in vitro. The Office Action alleges that although examples are given of Ad vectors with fiber proteins containing the C domain of S. aureus and one example of an Ad vector with an Fc-targeting ligand molecule, the specification doesn't contain an example of the claimed targeted recombinant adenovirus vector comprising both of these elements (plus a heterologous gene). Further the Office Action alleges that the specification does not teach a single adenovirus vector wherein the native tropism has been ablated and wherein the targeting ligand with specific high affinity for the cellular receptor has been incorporated into the capsid of the virus. The claims have been amended, rendering this objection moot.

Claims 1-3, 5-10 and 12-18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Furthermore, it alleges that the specification does not describe how a vector with a modified fiber protein, an immunoglobulin-binding domain, a gene encoding a Fc-ligand fusion protein, and a heterologous gene, once made, would of themselves thereby target the Ad vector via the claimed binding interactions. Specifically, that there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those Ad vectors that satisfy the functional limitations of the claims. The claims have been amended, rendering this objection moot.

The rejection is respectfully traversed for the following reasons.

Although the Applicants do not agree with the Examiner, in the interest of expediting prosecution, claim 1 has been amended to insert the limitations of claims 2 and 6. Specifically, it

is respectfully asserted that an enabling *disclosure* is all that is required. The applicant need not describe actual embodiments or examples. Indeed, an applicant need not have reduced the invention to practice prior to filing; the presence or absence of examples in a patent specification is only one factor in determining the extent to which claims, especially broad claims involving an unpredictable technology, are enabled.

Moreover, a prior art reference contains an enabling disclosure if a person of ordinary skill could have combined the description of the invention in the prior art reference with his own knowledge of the art to place himself in possession of the invention. It is respectfully submitted that the state of the art pertaining to the invention was not unpredictable at the time of filing the application and thus could have been relied on for guidance in practicing the claimed invention. Applicants respectfully submit that one of ordinary skill in the art can make and use the vector of the present invention by combining the teachings of the specification with what was known to one of ordinary skill in the art at the effective filing date.

As the specification points out, the present invention teaches a binary system wherein the virus and targeting ligand are each synthesized through natural biochemical pathways after which they self-associate into a stable complex (line 17, page 13). Example 2 illustrates design of the Ad5 fiber protein modified with the C domain of Staphylococcus aureus Protein A, and teaches a mechanism for attachment of targeting ligands to Ad particles. The C domain (Cd) is known to bind with high selectivity and affinity to the Fc domain of immunoglobulins (Ig). Therefore, Ad virions incorporating such Cd-modified fibers were expected to bind targeting ligands designed to contain an Fc domain. Indeed, Example 3 teaches modification of the HI-loop of Ad5 fiber and Example 4 teaches that the designed protein chimeras could be expressed at levels comparable with that of the wild type Ad5 fiber and that they possess structural and functional (Fc-binding capability) properties required for both the incorporation of these proteins into Ad virions and for binding to Fc-containing proteins.

Example 6 teaches design of a complementary ligand molecule, Fc-single chain antibody (scFv) fusion protein, that is capable of targeting the virus via association with its altered capsid. Furthermore, this example teaches that both components of the newly designed gene delivery system, the viral vector and the targeting ligand, were able to associate with each other. Strong binding of the Cd-modified vectors to the ligand is demonstrated compared to virtually no binding observed with the control Ad lacking C domain in the capsid. This proves the feasibility

of the formation of targeting vector complexes. As noted in thi example, other targeting ligands have been constructed such as the recombinant protein comprising the extracellular domain of human CAR as reported by Dmitriev (line 5, page 51) and recombinant protein Fc-CD40L as reported by Lo (line 14, page 51).

Example 7 teaches that all Cd-modified Ad were able to employ the Fc-G28.5 ligand for CD40-mediated infection, with no significant variations between the vectors. Examples 8 and 9 teach preparation of complexes of Ad with Fc-containing targeting ligands and demonstrate their ability to transduce, or infect, CD40-positive cells. Furthermore, Example 10 demonstrates in vitro transduction of primary human dendritic cells with the CD40-targeted vectors.

In summary, the modifications made to the claims as well as the examples discussed herein together serve to obviate the rejections since they clearly convey that the present invention is indeed enabled. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph are respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner is respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks herein, reconsideration and withdrawal of the restriction requirement are requested. Early and favorable consideration of the application on the merits, and early Allowance of the application are earnestly solicited.

The Commissioner is hereby authorized to charge any additionally required fee, or credit any overpayment in fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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